

ANTIHIISTAMINE/DECONGESTANT REGIMENS FOR TREATING RHINITIS

BACKGROUND OF THE INVENTION

Related Applications

5           The applicants wishes to claim the benefit of U.S. Provisional Patent Application No. 60/063,710, dated October 29, 1997, for REGIMEN FOR TREATING RHINITIS in the names of Robert E. Weinstein and Allan M. Weinstein.

Field of the Invention

10           The present invention relates to rhinitis treatment regimens, more particularly, to prepackaged therapeutic regimens for the symptomatic treatment of rhinitis which combine decongestant and antihistamine medications in a manner so as to avoid sedation when sedation is undesired  
15 and to avoid stimulation when stimulation is undesired.

The Prior Art

          Rhinitis refers to an inflammatory disorder of the nasal passages. The symptoms of rhinitis typically consist of sneezing, rhinorrhea, nasal congestion, and increased  
20 nasal secretions. Failure of treatment of rhinitis may lead to other disorders including infection of the sinuses, ears and lower respiratory tract.

          Two types of oral medication are commonly used to treat rhinitis: decongestants and antihistamines. Decongestants  
25 and antihistamines differ in mechanism of action, therapeutic effects, and side effects. It is common



histamine to histamine receptors in the nasal membranes. Antihistamines preemptively bind to histamine receptors and are effective only if given prior to histamine release (once histamine is released and binds to the receptor, it is too late). Although individuals typically take antihistamines after symptoms occur, it is more desirable to dose antihistamine so as to effect therapeutic activity in anticipation of the peak times of histamine release.

Individuals with rhinitis commonly experience peak symptoms in the morning hours on awakening, a time concomitant with peak histamine release and coinciding with peak exposure to airborne allergens which stimulate histamine release in sensitive individuals.

To improve upon the sedation of such older antihistamines, newer antihistamines with little or no sedation have more recently been developed.

The combining of decongestants and antihistamines utilizes two mechanistic approaches, and has been shown to offer more complete relief of rhinitis symptoms than therapy with either component alone. Consequently, many products have been formulated so that their dosage units contain both. While individuals are known to vary in their susceptibility to side effects, the incorporation of decongestant and sedating antihistamine into a single dosage unit represents an attempt to balance stimulation and sedation of the components. Consequently, some individuals

experience irritability and/or sedation with these combinations. Examples of commercial formulations containing decongestant and sedating antihistamine include:

1. CHLOR-TRIMETON® 4 hour Allergy/Decongestant which  
5 contains 4 mg of chlorpheniramine (sedating antihistamine)  
and 60 mg pseudoephedrine sulfate (stimulating  
decongestant), and which is recommended to be taken every 4  
to 6 hours (1/2 this dosage for children 6 to under 12);

2. CHLOR-TRIMETON® 12 hour Allergy/Decongestant which  
10 contains 8 mg of chlorpheniramine (sedating antihistamine)  
and 120 mg pseudoephedrine sulfate (stimulating  
decongestant), and which is recommended to be taken every 12  
hours (adults and children over 12 years of age only);

3. BROMFED® Tablets which contains 4 mg of  
15 brompheniramine (sedating antihistamine) and 60 mg  
pseudoephedrine sulfate (stimulating decongestant), and  
which is recommended to be taken every 4 to 6 hours (1/2  
this dosage for children 6 to under 12);

4. BROMFED® Capsules which contains 12 mg of  
20 brompheniramine (sedating antihistamine) and 120 mg  
pseudoephedrine sulfate (stimulating decongestant), and  
which is recommended to be taken every 12 hours (adults and  
children over 12 years of age only);

5. BENADRYL® Allergy Decongestant Tablets which  
25 contains 25 mg of diphenhydramine hydrochloride (sedating  
antihistamine) and 60 mg pseudoephedrine sulfate

(stimulating decongestant), and which is recommended to be taken by adults and children over 12 years of age every 4 to 6 hours, not to exceed 4 tablets in 24 hours; and

6. TAVIST-D® Tablets which contains 1.34 mg  
5 clemastine fumarate (sedating antihistamine) and 75 mg  
phenylpropanolamine hydrochloride (stimulating  
decongestant), and which is recommended to be taken every 12  
hours (adults and children over 12 years of age only).

More recently, formulations have been commercialized  
10 which incorporate both a decongestant and a non-sedating  
antihistamine into a single dosage unit. While such  
formulations offer the advantage in being non-sedating, such  
combinations might be expected to provoke a greater  
incidence of nighttime irritability and insomnia because the  
15 stimulating side effects of the decongestant are not  
attenuated by concomitant use of sedating antihistamine.  
Indeed, a 25% incidence of insomnia has been disclosed among  
users of the combination of non-sedating antihistamine  
terfenadine and pseudoephedrine. Examples of such  
20 formulations include:

1. SELDANE-D® Extended-Release Tablets which contains  
60 mg terfenadine (non-sedating antihistamine) and 120 mg  
pseudoephedrine hydrochloride (stimulating decongestant),  
and which is recommended to be taken every 12 hours (adults  
25 and children over 12 years of age);

2. CLARITIN-D® 24 HOUR Extended-Release Tablets which contains 10 mg loratidine (antihistamine) and 240 mg pseudoephedrine hydrochloride (decongestant) and, which is recommended to be taken every 24 hours (adults and children  
5 over 12 years of age); and

3. ALLEGRA-D™ which contains 60 mg fexofenadine (non-sedating antihistamine) and 120 mg pseudoephedrine hydrochloride (stimulating decongestant), and which is recommended to be taken every 12 hours (adults and children  
10 over 12 years of age).

U.S. Patent # 4,295,567, issued to Knudsen, teaches a regimen to avoid sedation from antihistamines when sedation is undesired. The Knudsen patent therefore does not apply to antihistamines which are not sedating. In accordance  
15 with Knudsen, prepackaged regimens for treating the symptoms of rhinitis have been commercialized, and employ decongestant for daytime and decongestant plus sedating antihistamine for night. Examples in accordance with Knudsen include:

20 1. DAYTIME & NIGHTTIME ACTIFED ALLERGY® which contains 30 mg pseudoephedrine (decongestant) in the daytime formulation, and 30 mg pseudoephedrine (decongestant) and 25 mg diphenhydramine (antihistamine) in the nighttime formulation; and

25 2. CONTAC DAY & NIGHT ALLERGY/SINUS® which contains 60 mg pseudoephedrine (decongestant) and 650 mg

acetaminophen (analgesic) in the daytime formulation, and 60 mg pseudoephedrine (decongestant), 50 mg diphenhydramine (antihistamine), and 650 mg acetaminophen (analgesic) in the nighttime formulation.

5       Regimens have also been commercialized which incorporate a decongestant for daytime and not for nighttime. An example of one such prepackaged regimen is SYN-RX™, which contains 60 mg pseudoephedrine HCL and 600 mg Guaifenesin in the day formulation, and 600 mg Guaifenesin  
10 in the nighttime formulation. These regimens avoid stimulation from decongestant at night, however lack antihistamine. Further, they neither contain medication which would be effective for rhinitis symptoms at night, nor anticipate peak symptoms of rhinitis in the morning hours on  
15 awakening.

While the problem of sedation with combined decongestant and sedating antihistamine treatment is addressed by Knudsen, the problem of nighttime irritability and insomnia is not. Indeed, all commercialized  
20 decongestant and antihistamine regimens according to Knudsen have the potential to cause irritability and insomnia at night.

Similarly, while the problem of sedation with combined decongestant and sedating antihistamine treatment are  
25 addressed in single entity combinations which employ decongestants and non-sedating antihistamines, the problem

of nighttime irritability and insomnia is not. Formulations which incorporate decongestant and non-sedating antihistamine into a single dosage unit are yet more likely to produce irritability and insomnia at night than  
5 formulations with sedating antihistamine.

It is well known that individuals with rhinitis utilize antihistamines and decongestants hundreds of millions of times a year. It is not uncommon for inappropriate choices to result in symptomatic worsening rather than improvement.  
10 Individuals often use sedating medication unknowingly or inappropriately. Decongestants taken at night not only produce insomnia in a sizable portion of users, but also daytime irritability, fatigue, and malaise from lack of rest. Users are known to mistakenly ascribe such symptoms  
15 to rhinitis rather than to medication. Professional as well as consumer confusion is widely encountered with these medications and unnecessarily negative consequences occur both by self-selection and prescription. There is a present need for preformulated regimens which advantageously use  
20 antihistamines and decongestants for rhinitis in a manner to circumvent this confusion, and to avoid both daytime sedation and nighttime stimulation.

Adherence to medication therapy and prevention of medication error are considerable medical problems and are  
25 improved with measures to establish simplicity, reduce confusion, and increase convenience. The proposed use of a



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multiplicity of dosage units as a regimen may be associated with dosage units being confused with each other, inadvertently switched, lost, misplaced, or ignored.

Another problem associated with treatment using a plurality  
5 of dosage units is the lack of indicia which distinguish the dosage units from each other and signify and verify their use together and readily available instructions for coordinating the medications. Individuals are known to lose instructions issued separate from the medication. Haphazard  
10 selection and organization of medications can result in treatment failure and in the patient's requiring additional medical attention involving time, expense, and personnel costs and effort to instruct and organize therapy. Cost factors and outcomes are being carefully considered in the  
15 current medical climate. Improvements in organization and teaching including devices and methods which would help patients be more cognizant of their proper therapeutic requirements are considered desirable in view of limitations in time and costs for medical personnel. Successful therapy  
20 for rhinitis is less costly than unsuccessful treatment which eventuates in complications or multiple clinic visits.

#### SUMMARY OF THE INVENTION

It is therefore an object of the present invention to utilize decongestants and antihistamines in formulations so  
25 as to provide regimens for the treatment of rhinitis that avoid sedation during the day and that also avoid

stimulation at night. The terms "day" and "night" are intended to be synonymous with times when sedation is considered undesirable, such as when awake, and with times when stimulation is considered undesirable, such as bedtime, respectively, as well as literally daytime and nighttime, in that such times vary in accordance with the schedule of the individual.

It is another object to reduce confusion in the use of antihistamines and decongestants for the treatment of rhinitis.

The devising of such formulations and instructions for the use of such formulations requires pharmaceutical expertise and requires understanding of the actions, side effects, and pharmacokinetics of antihistamines, decongestants, and other formulated components, including components which effect the bioavailability of the active ingredients, as well as determination of the suitability of the components' use together. It is therefore another object of the present invention to provide a user with an expertly devised regimen.

It is a further object to provide a method and device for organizing, storing, and coordinating regimens for the treatment of rhinitis for the purpose of convenience in using such regimens by providing such regimens in a prepackaged container which incorporates coordinating indicia and instructions.

It is a further object to provide regimens which provide dosing of antihistamine in accordance with its kinetics so as to achieve histamine receptor binding in the morning hours, at the conventional time of awakening, which  
5 such scheduling is desired.

a It is a <sup>preferred</sup> ~~further~~ object to provide a user with an therapeutic combination of decongestant and antihistamine during the day, either by single nighttime dosing of sedating antihistamine which is suitable with respect to its  
10 half-life, duration of action, and duration of side effect, or by utilization of non-sedating antihistamine.

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The present invention provides for a prefilled, unifying dispensing container containing at least two modules of different dosage units for the treatment of  
15 rhinitis, indicia for distinguishing the dosage units and signifying their use together, and coordinating instructions for their use. The container can have one of any number of forms, including, but not limited to, a box with the dosages in bottles, a blister package, a box of individual blister  
20 packages, or a box of pouches.

There are at least two different dosages combining to form a regimen for the treatment of rhinitis. The dosages are combinations of medications that include antihistamine and nasal decongestant. One dosage is for administration  
25 when sedation is not desired and the other is for administration when stimulation is not desired. There are a

number of possible combinations of decongestants and antihistamines presently available that can be employed in the present invention. Other medications, such as analgesics, may be incorporated into the dosages.

5 Other objects of the present invention will become apparent in light of the following drawings and detailed description of the invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

For a fuller understanding of the nature and object of  
10 the present invention, reference is made to the accompanying drawings, wherein:

Fig. 1 is a plan view of one embodiment of the present invention;

Fig. 2 is a top view of another embodiment of the  
15 present invention;

Fig. 3 is a plan view of a third embodiment of the present invention; and

Fig. 4 is a front view of a fourth embodiment of the present invention.

#### 20 DETAILED DESCRIPTION

The present invention provides for a prefilled, unifying dispensing container containing at least two modules of different dosage units for the treatment of rhinitis, indicia for distinguishing the dosage units and  
25 signifying their use together, and coordinating instructions for their use. It is to be understood that either single or

multiple modules of each dosage unit are contained. The dosage units may be in the form of tablet, pill, capsule, caplet, powders, liquids, gels, some of which may require reconstituting, or any generally recognized oral form of medication.

Referring to the drawings, it will be understood that while preferred embodiments of the invention have been illustrated and described, the invention is not limited to such embodiments. Changes and additions may be made therein and thereto without departing from the spirit of the invention.

Embodiments of the unifying container are depicted in Figs. 1-4. Fig. 1 depicts a support package 10 containing multiple dosages of two different dosage units 12, 14 in tablet form 50 in blister packaging 52. Fig. 2 depicts a support package 20 which houses two modules in the form of bottles 22, 24 containing different dosage units, which can be in either liquid form or solid form. Fig. 3 depicts a support package 30 with a single dosage unit 32 for morning and a single different dosage unit 34 for night. Fig. 4 depicts a support package 40 which is manufactured to house a multiplicity of daytime modules in the form of pouches 42 and a multiplicity of nighttime modules in the form of pouches 44. In each of the four depicted configurations, the support package has specific provision for supporting the dosage units in physical accord with indicia 16, 26, 36,

46. The indicia manufactured with the support package distinguishes between the dosage units by means of wording, color, shape symbol, or other means known in the art. The indicia, by its presence, also indicates the suitability of the dosage units for use with each other. The support package incorporates coordinated administration instructions 18, 28, 38, 48 which also indicate the suitability of the dosage units for use with each other, and instruct coordination of the dosage units as a regimen.

Although the embodiments specifically described herein have two dosage modules, packaging containing other numbers of modules are also within the scope of this invention. The packaging may be adapted by widening the packaging and increasing the number of modules and indicia. Additionally, the packaging may be in any geometric configuration.

The packaging contains combinations of medications, which include nasal decongestants and antihistamines, that comprise a regimen for treating rhinitis. Specifically, the packaged medication is comprised of at least two dosage

units, one for administration when sedation is not desired, as, for example, during the day, and one for administration when stimulation is not desired, as, for example, at night.

The non-sedating dosage unit may be formulated to contain non-sedating antihistamine and/or decongestant, but not

sedating antihistamine. The non-stimulating dosage unit may be formulated to contain sedating or non-sedating

antihistamine, but not stimulating nasal decongestant. The regimen is devised utilizing a combination of dosage units which are favorable for use with each other, particularly with regard to pharmacokinetic and therapeutic

5 characteristics. It is possible to formulate these regimens with presently available dosage units as well as with newly formulated dosage units. Examples of regimens, some of which employ presently available dosage units, are described below.

10       Example 1: 120 mg pseudoephedrine hydrochloride (stimulating decongestant) and 5 mg loratidine (non-sedating antihistamine) to be taken in the morning, and 5 mg loratidine to be taken at bedtime. Limiting pseudoephedrine dosing to the day avoids stimulation and insomnia at night

15 when stimulation is undesired. Use of the non-sedating antihistamine, loratidine avoids sedation during the day. Loratidine is known to have a long half-life, exerting an antihistamine effect 1 to 3 hours after dosing, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours.

20 An effective daytime combination of decongestant and antihistamine would result from the dosing of both decongestant and non-sedating antihistamine in the morning.

Example 2: 120 mg pseudoephedrine hydrochloride (stimulating decongestant) to be taken in the morning and 10

25 mg loratidine (non-sedating antihistamine) to be taken at bedtime. In this instance, loratidine is dosed at bedtime

and reaches a peak efficacy in the early morning hours, a time when symptoms typically peak. Although antihistamine is not dosed during the day, an effective daytime combination of decongestant and antihistamine results from the dosing of decongestant in the morning and loratidine at night because of the 24-hour duration of the antihistamine affect of loratidine.

Example 3: 120 mg pseudoephedrine sulfate (stimulating decongestant) and 60 mg of fexofenadine (non-sedating antihistamine) to be taken in the morning, and 60 mg of fexofenadine to be taken in the evening. Limitation of pseudoephedrine dosing to the day avoids stimulation and insomnia at night when stimulation is undesired. Use of the non-sedating antihistamine fexofenadine avoids daytime sedation. The 12-hour duration of fexofenadine requires a daytime dosing to achieve an effective daytime combination of antihistamine and decongestant. Bedtime dosing of fexofenadine anticipates early morning histamine release.

Example 4: 60 mg pseudoephedrine sulfate (stimulating decongestant) to be taken in the morning and afternoon, and 4 mg of chlorpheniramine (sedating antihistamine) to be taken at bedtime. Despite the traditional, and still current, indication for 4 to 6 hour dosing for chlorpheniramine, a single dose has more recently been shown to inhibit the symptoms of rhinitis for more than 24 hours. Maximal sedation occurs approximately 3 to 4 hour



after dosing and sedation persists not longer than 6 to 8 hours following dosing. Notably, the short duration of sedation in relation to the longer duration of symptom suppression favors dosing of chlorpheniramine at bedtime as a way to anticipate peak morning histamine release, and effectively confer combined antihistamine and decongestant activity during the day without sedation and without dosing of sedating antihistamine during the day. The limiting of pseudoephedrine dosing to day avoids the potential for stimulation and insomnia at night.

Example 5: 35 mg phenylpropanolamine (stimulating decongestant) to be taken in the morning and late afternoon, and 4 mg of chlorpheniramine (sedating antihistamine) to be taken at bedtime. This regimen is essentially the same as that of Example 4, substituting the decongestant phenylpropanolamine for pseudoephedrine.

In addition to antihistamines and decongestants, other therapeutic ingredients for the treatment of rhinitis may be formulated if desired. For example, analgesics such as salicylates and acetophenamin may be considered for inclusion in such formulations and are within the scope of the present invention.

These examples do not constitute an exhaustive list of potential combinations, and variations and modifications may be made by those of ordinary skill in the art.

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Other variations may occur to those skilled in the art which are within the scope of the invention as set forth in the appended claims. Those of skill in the art may also recognize modifications to these presently disclosed

5 embodiments. These variations and modifications are meant to be covered by the spirit and scope of the present claims.

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